

Example 12 Film coating of Levodopa-Carbidopa Pellets with Bioadhesive Polymer, Spheromer™ III, Lot # 510-098

Levodopa, carbidopa, and levodopa-carbidopa pellets were film-coated with a bioadhesive polymeric composition, Spheromer™ III. Bioadhesive Spheromer™ III and optionally a functional polymer, or a non-functional polymer, and optionally pharmaceutically acceptable excipients, were dissolved in methanol. The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 35°C±2°C. The pellets were pre-warmed at 35°C for 2-5 min and after film-coating were post-dried at 30°C for 15-30 min. Alternatively, pellets were coated in a Fluid Air Model 5 fluid bed processor, equipped with a Wurster insert, operating at an inlet air flow rate of 70 cfm (cubic foot per minute) and an inlet air temperature of 35°C. The pellets were pre-warmed at 40°C for 5-7 min and after film-coating were post-dried at 35°C for 30 min.

Composition of Spheromer™ III Coating Solution, Lot # 511-098

Ingredients	Weight %	Weight (g)
Spheoromer™ III	94.7	71
Poloxamer 188 (Lutrol® F68), NF	5.3	4
Methyl alcohol, NF	*	(1,500 mL)
Total	100.0	150

a. Methyl alcohol is removed during the coating/drying process.

Example 13 Film coating of Levodopa Pellets with Bioadhesive Polymer, Spheromer™ III, and Hydroxypropylcellulose (HPC-SSL), Lot # 511-092

One thousand grams of levodopa pellets, lot # 510-095, were film-coated in a Fluid Air Model 5 fluid bed processor, equipped with a Wurster insert, in accordance with the method described in Example 12. The composition of the coating solution is given below. Spheromer™ III and Hydroxypropylcellulose (HPC-SSL) were dissolved in methanol and sprayed onto the fluidized pellets to obtain a 12% weight gain on pellets.

Composition of Spheromer™ III/Hydroxypropylcellulose (HPC-SSL) Coating Solution, Lot # 511-092

Ingredients	Weight %	Weight (g)
Spheoromer™ III	80.0	120
Hydroxypropylcellulose (HPC SSL), NF	20.0	30
Methyl alcohol, NF*	~	(3,000 mL)
Total	100.0	150

* Methyl alcohol is removed during the coating/drying process.

Example 14 Production of Carbidopa Granules with Low Shear Granulation, Lot # 511-101

Carbidopa granules were produced with low shear granulation method consisting of the following processes:

- (1) Weighing carbidopa, optionally a bioadhesive polymer composition, and pharmaceutically acceptable excipients.
- (2) Blending carbidopa, and optionally a bioadhesive polymer composition, with pharmaceutically acceptable excipients in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a dry mix.
- (3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluid was mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, an alcohol, a hydro-alcoholic mixture, or an alcoholic or hydro-alcoholic solution of a polymeric composition.
- (4) Drying the granulation from step (3) in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of 50°C. Alternatively, the granulation from step (3) was dried in a Precision gravity oven, operating at 50°C, for 8-24 h.
- (5) Screening and classifying the dried granules from step (4) through a stack of stainless steel sieves, U.S. standard mesh sizes 20 and 60, using a mechanical sieve shaker, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of granular formulations were analyzed, and classified granules ranging from 0.25 mm (mesh # 60) to 0.85 mm (mesh # 20) were selected for future experimentation.

The weight and composition of granules are given below. Carbidopa was blended with inactive excipients for 5 min. The carbidopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was blended for an additional 5 min and then dried in a Precision gravity oven at 50°C for 8 - 48 hours. The dried granules were screened and particles smaller than 0.85 mm were selected for future experimentation.

Weight and Composition of Carbidopa Granules, Lot # 511-101

Ingredients	Weight %	Weight (g)
Carbidopa monohydrate, USP	52.0	104
Microcrystalline cellulose (Emocel® 90 M), NF	23.5	47
Mannitol (Mannogem™ Powdered), USP	13.5	27
Hydroxypropylcellulose (HPC-SSL), NF	5.0	10
Croscarmellose sodium (Ac-Di-Sol®), NF	5.0	10
Citric acid, anhydrous, USP	1.0	2
Total	100.0	200

Example 15 Preparation of Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules, Lots # 510-099 & 510-100

Levodopa pellets (lot # 510-095), Spheromer™ III-coated levodopa-carbidopa pellets (lot # 510-098), HPC-SSL/Spheromer™ III-coated levodopa pellets (lot # 511-092), and carbidopa granules (lot # 511-101) were encapsulated in 00-size hard gelatin capsules. Each capsule contained 200 mg levodopa and 50 mg carbidopa anhydrous. The composition of multiparticulates in each capsule formulation is given below.

Composition (mg) of Multiparticulate Capsule Formulations, Lot # 510-099 & 510-100

Components	Lot #	510-099	510-100
Levodopa Pellets	510-095	80	80
Spheroner III-coated Levodopa-Carbidopa Pellets	510-098	340	255
HPC-SSL/Spheroner™ III-coated Levodopa	511-092	-	90
Carbidopa Granules	511-101	20	40
Total (mg per capsule)	-	440	

Example 16 Preparation of Combined Pramipexole 0.375 mg Extended-Release Pellets and Levodopa-Carbidopa 200 mg/50 mg Immediate/Controlled-Release Multiparticulates as a Delayed-Release Capsule Formulation

Pramipexole extended-release pellets, lot # 601-048 (from Example 9), containing 0.375 mg pramipexole, and levodopa-carbidopa immediate/controlled-release multiparticulates, lot # 510-099 (from Example 15), containing 200 mg levodopa and 50 mg carbidopa, were co-encapsulated in two-piece hard gelatin capsules. These capsules were sealed at the junction of cap and body using an aqueous gelatin solution and then coated with 1.6% (w/w) Opadry® Clear (YS-1-19025-A). The Opadry-coated capsules were top-coated with an enteric coating composition, Acryl-EZE™ White, in a pan coater (O'Hara Technologies Labcoat System). The capsules were sprayed with a 10% (w/v) solution of Acryl-EZE™ White in ethanol and water mixture (90:10 v/v) so as to achieve a final weight gain of 5-12% (w/w).

The bioadhesive pramipexole and levodopa-carbidopa pellets may be optionally top-coated with bioadhesive Spheroner™ I polymer, a hypromellose polymer, a hydroxypropylcellulose polymer, or a polyvinyl alcohol polymer to a weight gain of 2-5% (w/w).

Example 17 Preparation of Pramipexole 0.375 mg Delayed/Extended-Release Capsule Formulation, Lot # 601-056

Pramipexole extended-release pellets, lot # 601-048 (from Example 9) containing 0.375 mg pramipexole were encapsulated in a size 2 hard shell gelatin capsule. These capsules were sealed at the junction of cap and body using an aqueous gelatin solution and coated with 1.6 % Opadry® Clear (YS-1-19025-A). The Opadry-coated capsules were then

coated with an enteric coating composition, Acryl-EZE™ White, in a pan coater (O'Hara Technologies Labcoat System). The capsules were sprayed with a 10% (w/v) solution of Acryl-EZE™ White in ethanol and water mixture (90:10 v/v) so as to achieve a final weight gain of 5-12% (w/w).

The unit dose composition of a pramipexole 0.375 mg delayed/extended-release capsule formulation is given below.

Unit Dose Composition of Pramipexole 0.375 mg Delayed/Extended-Release Capsule Formulation

Components	Weight (%)	Weight (mg)
Pramipexole Dihydrochloride Monohydrate, USP	0.13	0.375
Mannitol (Mannogem™ Powdered), USP	21.45	60.93
Microcrystalline Cellulose (Emcocel® 90M), NF	9.90	28.13
Acryl-EZE™ White (93O18509)	8.14	23.12
Opadry® Clear (YS-1-19025-A)	3.13	8.90
Ethylcellulose (Ethocel™ Std 10 FP Premium), NF	2.91	8.28
Spheroner™ III	1.81	5.14
Hydroxypropyl Cellulose (HPC-SSL), NF	1.65	4.69
Poloxamer 188 (Lutrol® F 68), NF	0.10	0.27
Dibutyl Sebacate, NF	0.09	0.25
Gelatin Capsule, Size 2	50.69	144.00
Total	100.00	284.085

Example 18 Preparation of Combined Pramipexole 0.375 mg Delayed/Extended-Release Pellets and Levodopa-Carbidopa 200 mg/50 mg Immediate/Controlled-Release Multiparticulates as a Capsule Formulation

Pramipexole delayed/extended-release pellets, lot # 601-056 (from Example 17), containing 0.375 mg pramipexole, and levodopa-carbidopa immediate-controlled-release multiparticulates, lot # 510-099 (from Example 15), containing 200 mg levodopa and 50 mg carbidopa, were co-encapsulated in two-piece hard gelatin capsules.

The bioadhesive pramipexole and levodopa-carbidopa pellets may be optionally top-coated with bioadhesive Spheroner™ I polymer, a hypromellose polymer, a hydroxypropylcellulose polymer, or a polyvinyl alcohol polymer to a weight gain of 2-5% (w/w).

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All patents, publications, and other references cited above are hereby incorporated by reference in their entirety.

We Claim:

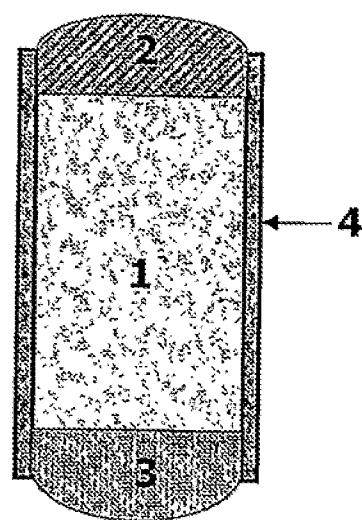
1. A delayed-release (DR) pramipexole pharmaceutical composition in an orally deliverable form, comprising an enteric coating, a pramipexole core, and pharmaceutically acceptable carriers and excipients, wherein the enteric coating substantially eliminates the release and/or absorption of pramipexole in the upper gastrointestinal (GI) tract.
2. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein pramipexole is first released and/or absorbed in intestine.
3. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the enteric coating delays the release of pramipexole by at least about 1.5 – 2 hours.
4. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the enteric coating is selected from: cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal collophorium, carboxymethyl ethylcellulose, Spheroner III, Spheroner IV, co-polymerized methacrylic acid / methacrylic acid methyl esters selected from: EUDRAGIT® L12.5, L100, EUDRAGIT® S12.5, S100, EUDRAGIT® L30D55, EUDRAGIT® FS30D, EUDRAGIT® L100-55, EUDRAGIT® S100 (Rohm Pharma), KOLlicoat® MAE30D and 30DP (BASF), ESTACRYL® 30D (Eastman Chemical), AQUATÉRIC® and AQUACOAT® CPD30 (FMC)), Acryl-EZE™ White, or equivalents thereof.
5. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the enteric coating becomes soluble around pH 6.8.
6. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the pramipexole pharmaceutical composition comprises a pramipexole salt.

7. The delayed-release pramipexole pharmaceutical composition of claim 6, wherein the pramipexole salt is pramipexole dihydrochloride monohydrate.
8. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the pramipexole core is formulated as an immediate release (IR) composition.
9. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the pramipexole core is formulated as an extended release (XR) composition.
10. The delayed-release pramipexole pharmaceutical composition of claim 9, wherein the XR composition is prepared by coating pramipexole-layered inert pellets with a release-controlling polymer.
11. The delayed-release pramipexole pharmaceutical composition of claim 10, wherein the release-controlling polymer is ethylcellulose-based.
12. The delayed-release pramipexole pharmaceutical composition of claim 10, wherein the release-controlling polymer is selected from: EUDRAGIT® RL; EUDRAGIT® RS; cellulose derivatives selected from: ethylcellulose aqueous dispersions (AQUACOAT®, SURELEASE®), hydroxyethyl cellulose, hydroxypropyl cellulose, or hydroxypropyl methylcellulose; polyvinylpyrrolidone; polyvinylpyrrolidone / vinyl acetate copolymer; OPADRY®, or equivalents thereof.
13. The delayed-release pramipexole pharmaceutical composition of claim 9, which is formulated to provide an effective dose over at least 4 – 20 hours or 8 – 16 hours after administration to the patient.
14. The delayed-release pramipexole pharmaceutical composition of claim 13, wherein the effective dose is about 800 – 1800 pg/mL for Parkinson's Disease treatment.
15. The delayed-release pramipexole pharmaceutical composition of claim 1, wherein the pramipexole core comprises an XR portion and an IR portion.
16. The delayed-release pramipexole pharmaceutical composition of claim 15, wherein the XR portion and the IR portion are both multiparticulate beads / pellets embedded within an inactive dissolvable / disintegratable matrix.
17. The delayed-release pramipexole pharmaceutical composition of claim 15, wherein the XR portion and the IR portion are each a symmetric or asymmetric portion of the pramipexole core.

18. The delayed-release pramipexole pharmaceutical composition of claim 15, wherein the XR portion is partially or completely covered by a rate-controlling coating that controls the release rate of the XR portion.
19. The delayed-release pramipexole pharmaceutical composition of claim 1, which is formulated as a once-a-day composition.
20. The delayed-release pramipexole pharmaceutical composition of claim 19, wherein the once-a-day composition contains about 0.375 mg, 0.5 mg, 1.0 mg, 1.5 mg, 3.0 mg, or 4.5 mg of pramipexole dihydrochloride monohydrate, or equivalent thereof.
21. The delayed-release pramipexole pharmaceutical composition of claim 1, further comprising a bioadhesive layer that selectively adheres to the lower GI tract.
22. The delayed-release pramipexole pharmaceutical composition of claim 21, wherein the bioadhesive layer comprises polymeric materials selected from polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric acid), poly(maleic acid), polycarbonates, polyalkylenes, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polysiloxanes, polystyrene, poly(lactide-co-glycolide), blends and copolymers thereof.
23. The delayed-release pramipexole pharmaceutical composition of claim 1, which, upon administering to an individual, does not induce at least one undesirable side-effect selected from: nausea, emesis, insomnia, hallucination, somnolence, constipation, and gastric and/or intestinal complication at a severity induced by administration of an immediate-release formulation of the same dosage.
24. The delayed-release pramipexole pharmaceutical composition of claim 23, wherein the nausea or emesis results from a locally mediated gastric irritation triggered by the immediate release formulation.
25. The delayed-release pramipexole pharmaceutical composition of claim 1, which has substantially the same bioavailability and/or maximum blood concentration (C_{max}) compared to a pramipexole pharmaceutical composition of equivalent dosage without the enteric coating.

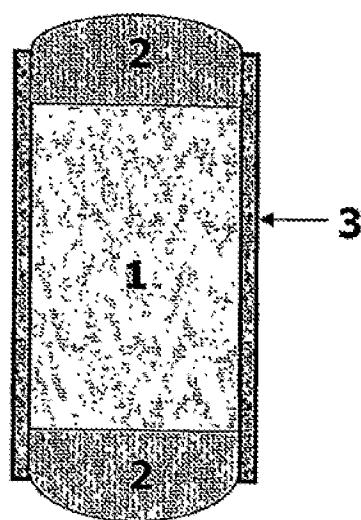
26. The delayed-release pramipexole pharmaceutical composition of claim 1, which is suitable for human administration, or for veterinary treatment of a non-human mammal.
27. A method of preparing a pramipexole pharmaceutical composition, comprising coating pramipexole with an enteric coating that substantially eliminates the release and/or absorption of pramipexole in the upper gastrointestinal (GI) tract.
28. A method of treating Parkinson's Disease in an individual, comprising administering to the individual a delayed-release pramipexole pharmaceutical composition of claim 1.

FIG. 1A



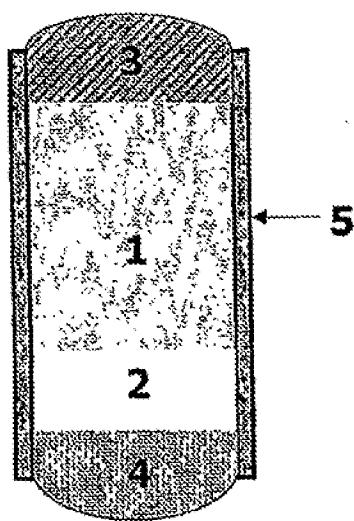
1. Slow Eroding Active Core
2. Insoluble Plug
3. Enteric Polymeric Plug
4. Bioadhesive Polymeric Cylinder

FIG. 1B



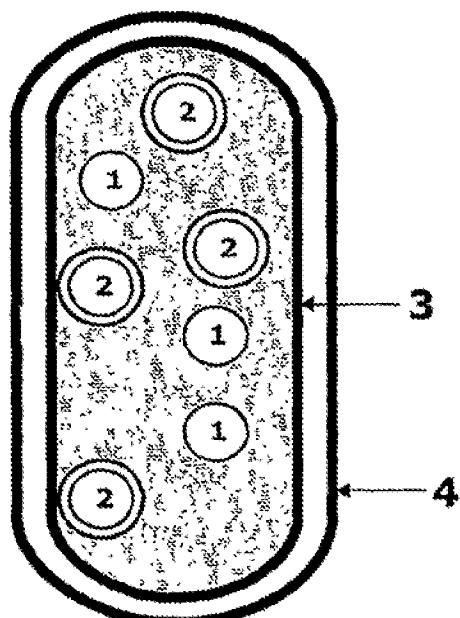
1. Slow Eroding Active Core
2. Enteric Polymeric Plug
3. Bioadhesive Polymeric Cylinder

FIG. 1C



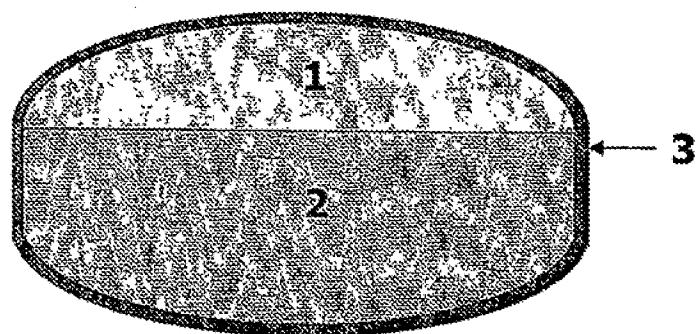
1. Slow Eroding Active Core
2. Immediate Release Active Core
3. Insoluble Plug
4. Enteric Polymeric Plug
5. Bioadhesive Polymeric Cylinder

FIG. 1D



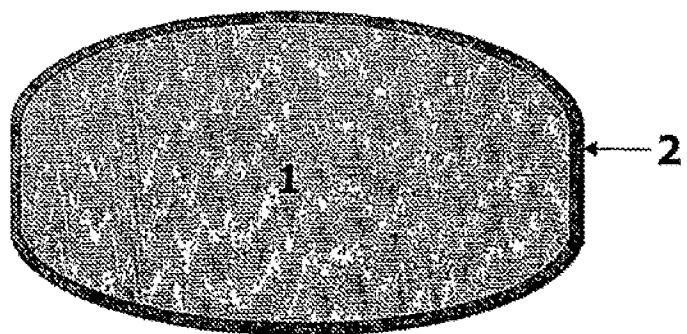
1. Immediate Release Beads/Pellets
2. Controlled Release Beads/Pellets
3. Hard Gelatin Capsule
4. Enteric Coating

FIG. 1E



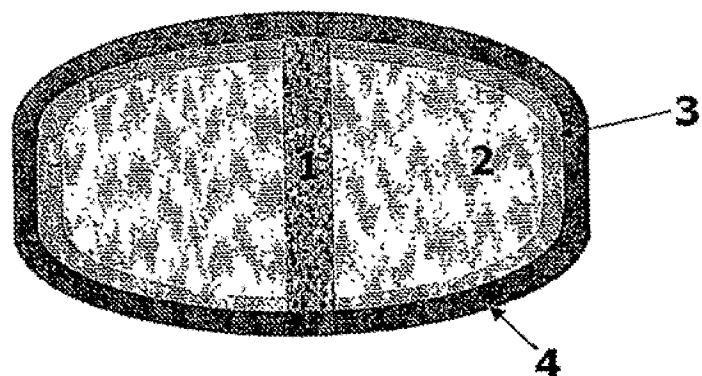
1. Immediate Release Active Layer
2. Controlled Release Active Layer
3. Enteric Coating

FIG. 1F



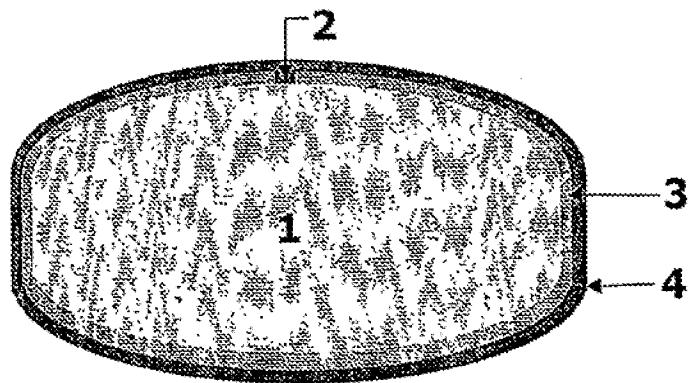
1. Slow Eroding or Non-eroding Active Matrix Core
2. Enteric Coating

FIG. 1G



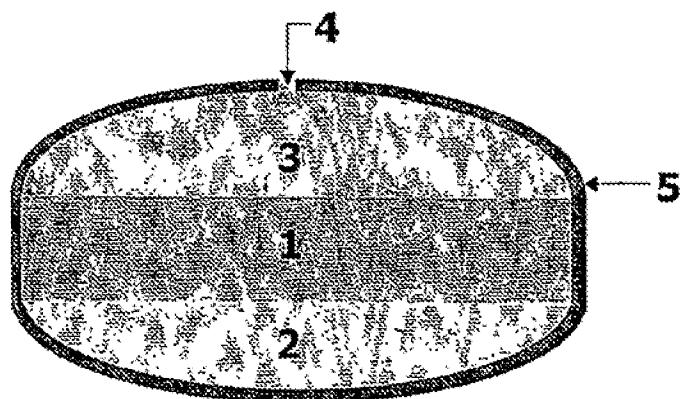
1. Immediate Release Active Core
2. Controlled Release Active Core
3. Rate Controlling Coating
4. Enteric Coating

FIG. 1H



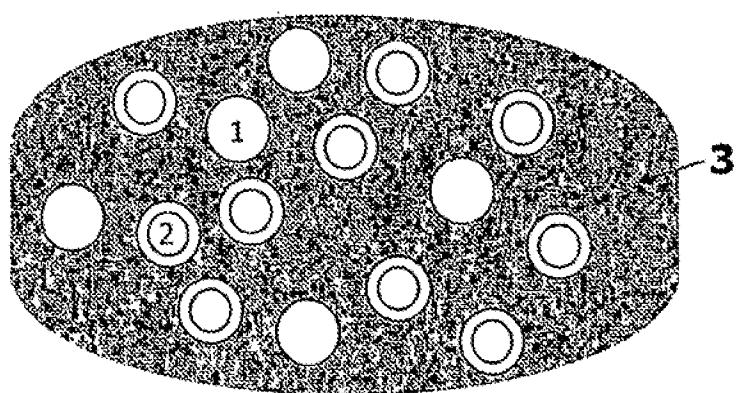
1. Active Core
2. Orifice
3. Semi-permeable Coating
4. Delayed Release Coating/Enteric Coating

FIG. 11



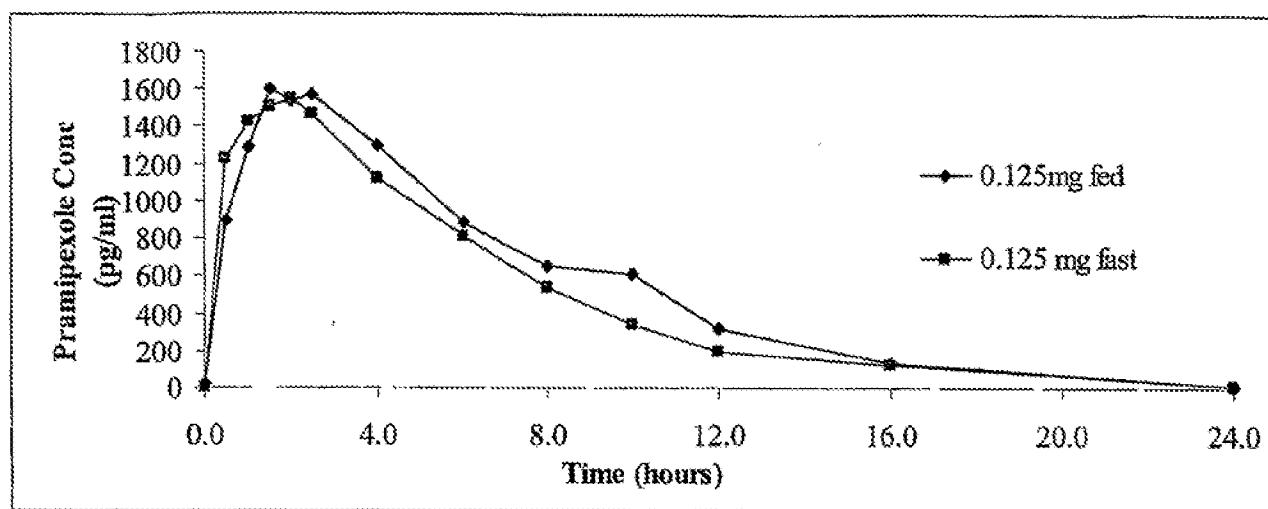
1. Active Core
2. Push Layer
3. Delayed Release (non-active) Layer
4. Orifice
5. Semi-permeable Coating

FIG. 1J



1. Immediate Release Beads
2. Controlled Release Beads
3. Enteric Polymer Material - (along with compression enhancers and fillers)

FIG. 2



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FIG. 3

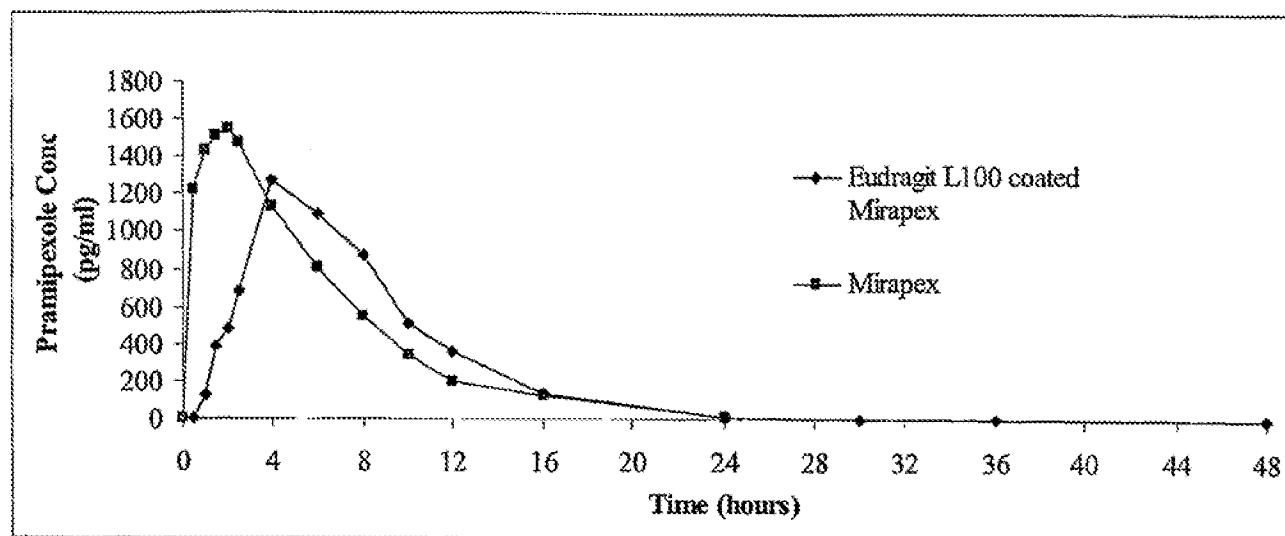


FIG. 4

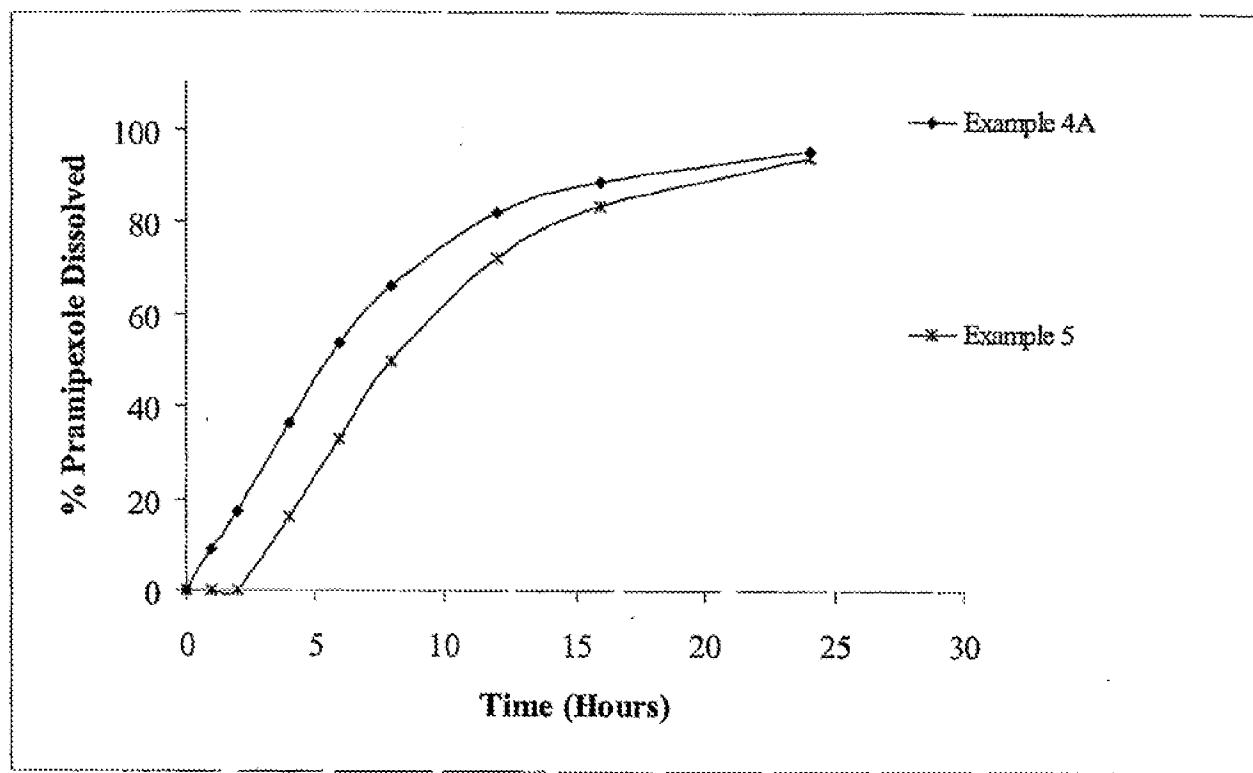


FIG. 5

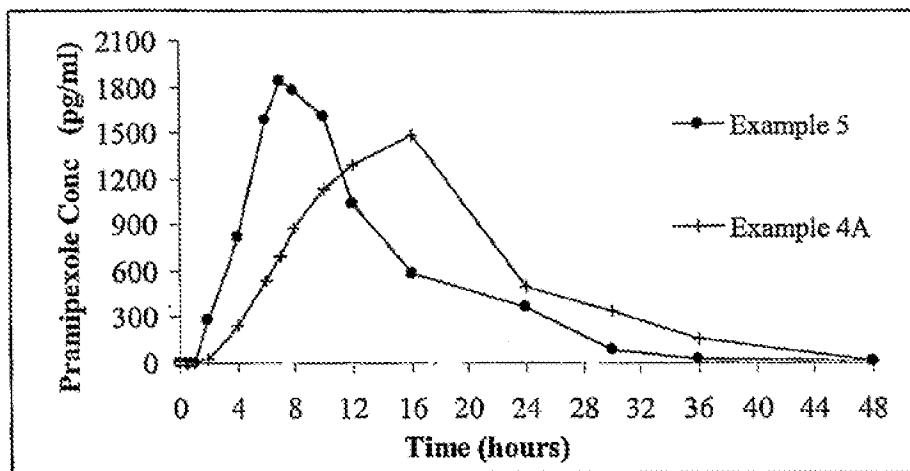


FIG. 6

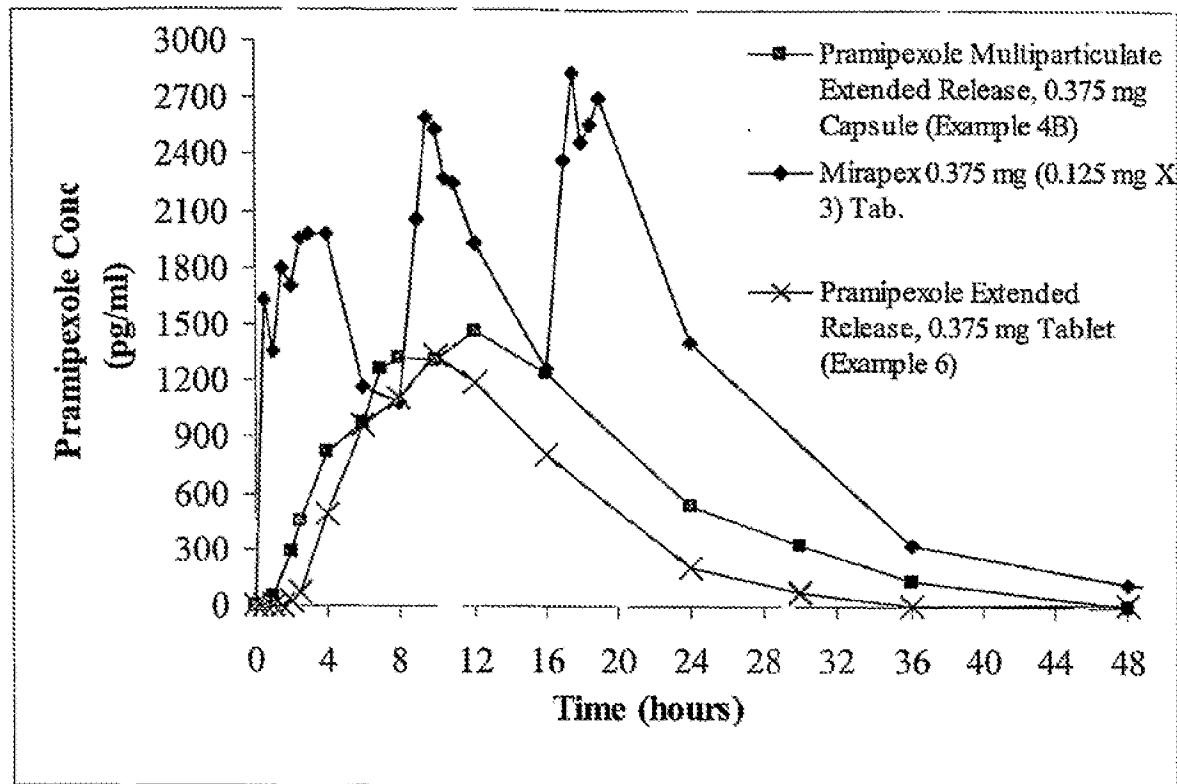


FIG. 7

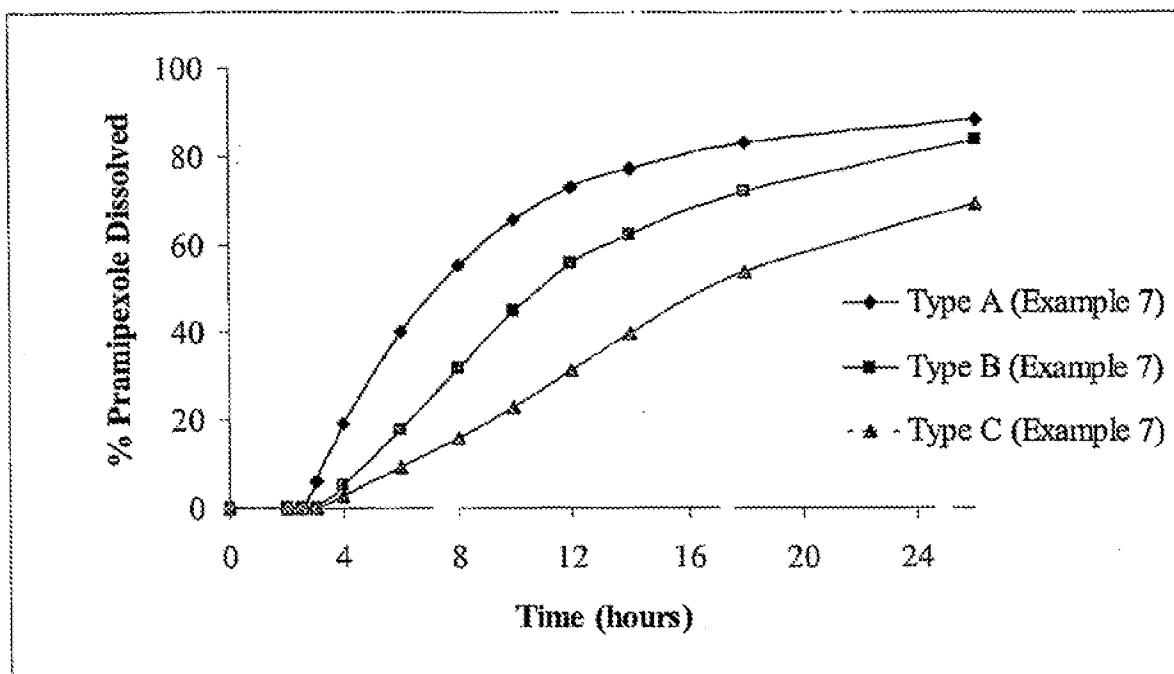


FIG. 8

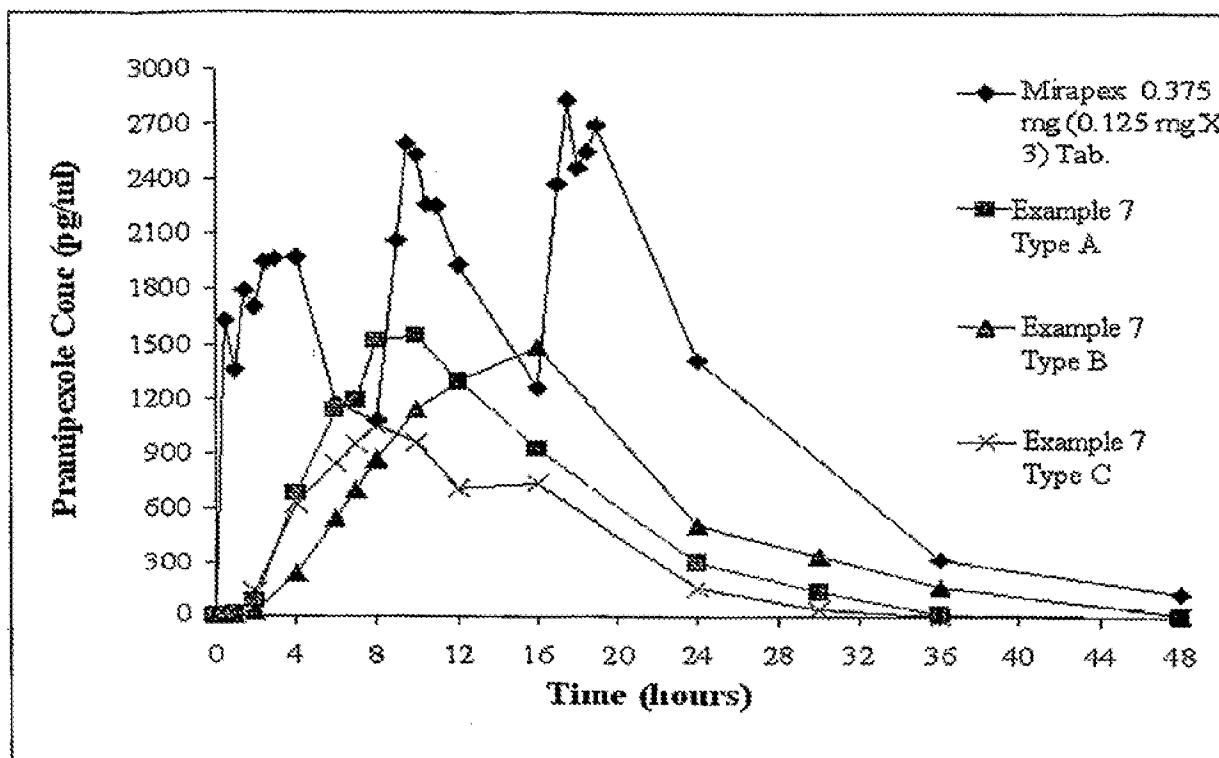


FIG. 9A

Mean Pramipexole plasma concentration graphs for treatments A and D

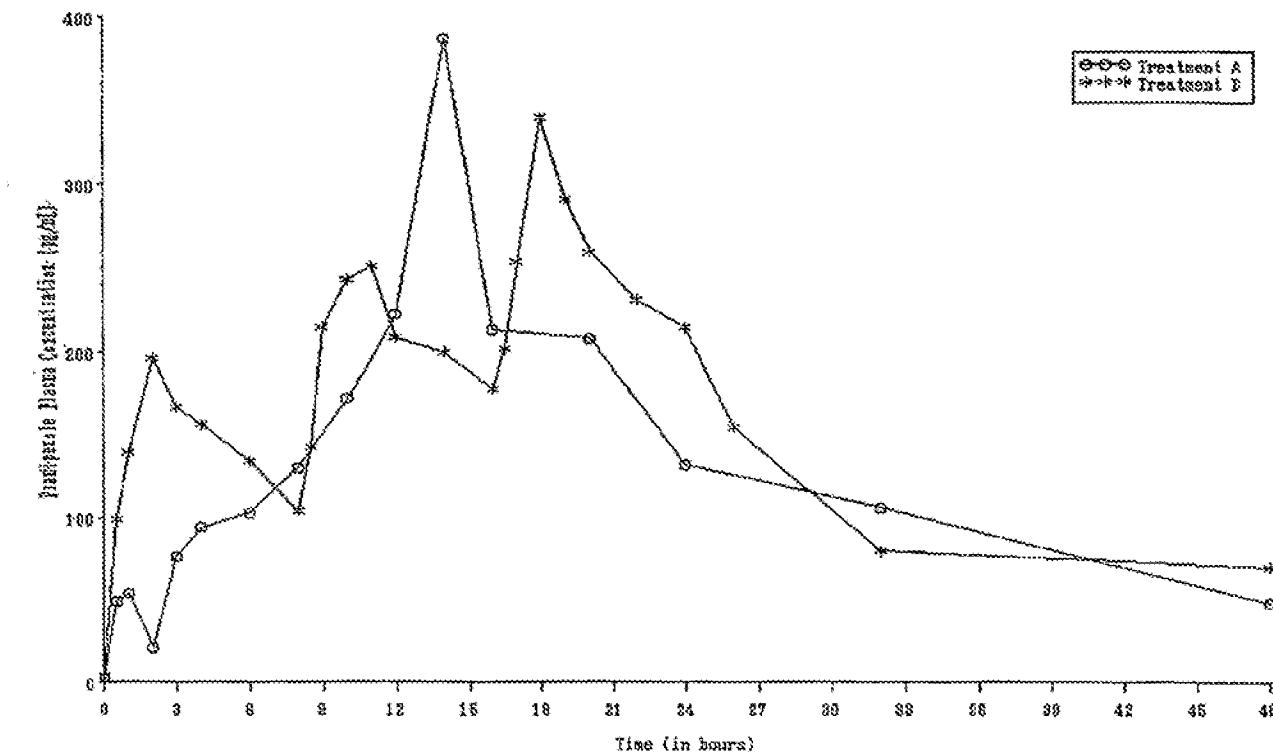


FIG. 9B

Mean Pramipexole plasma concentration graphs for treatments B and D

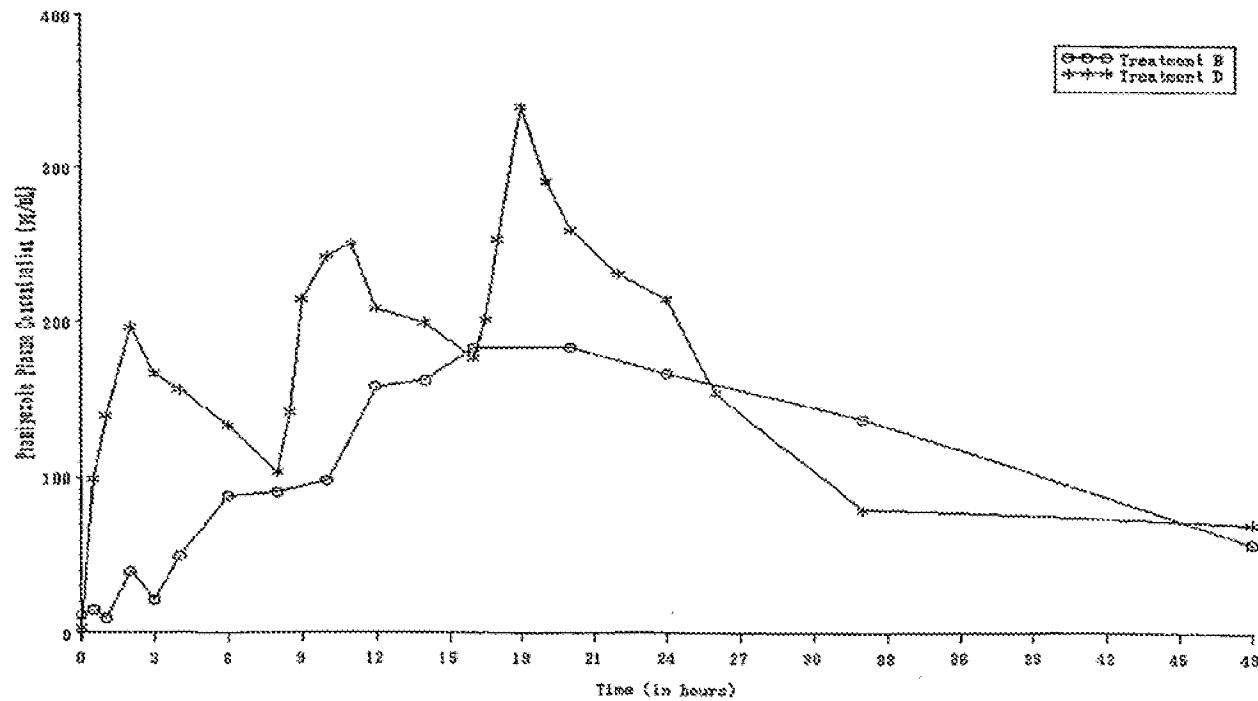


FIG. 9C

Mean Pramipexole plasma concentration graphs for treatments C and D

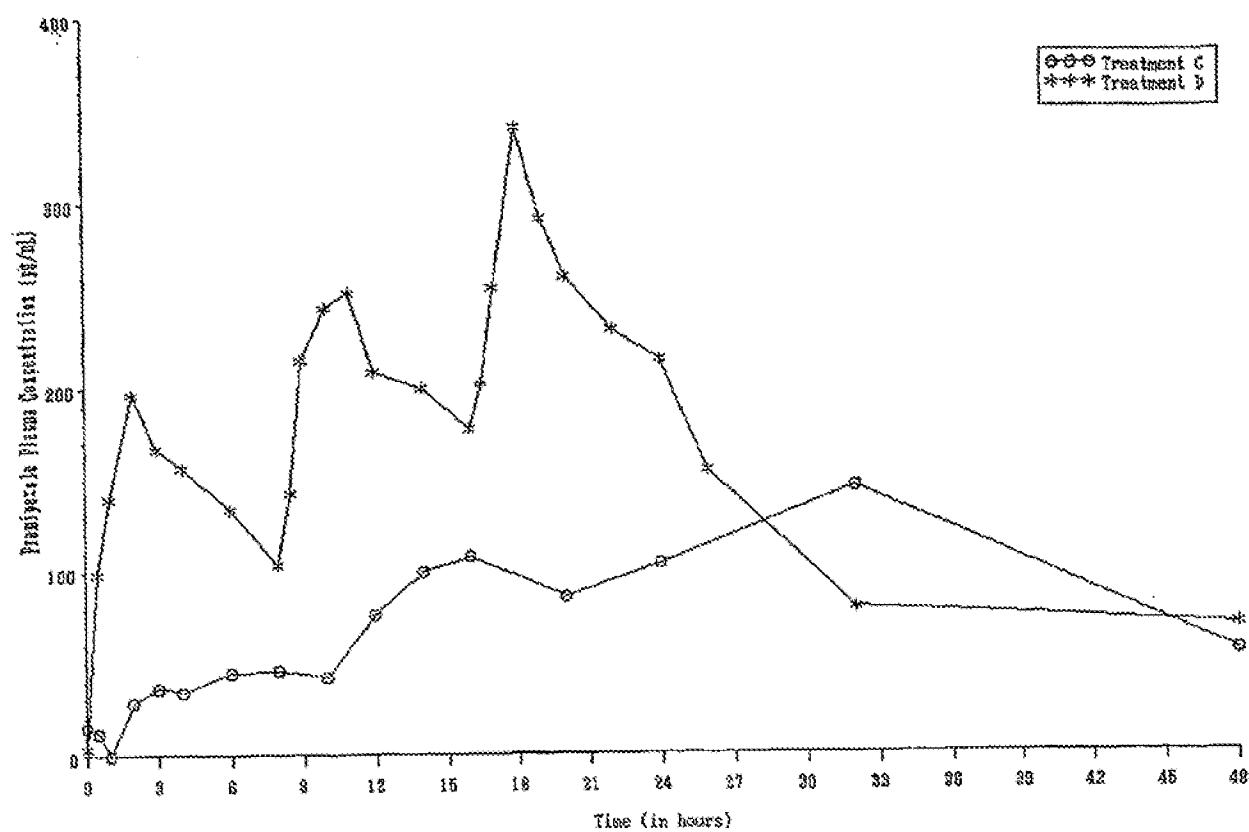


FIG. 10A

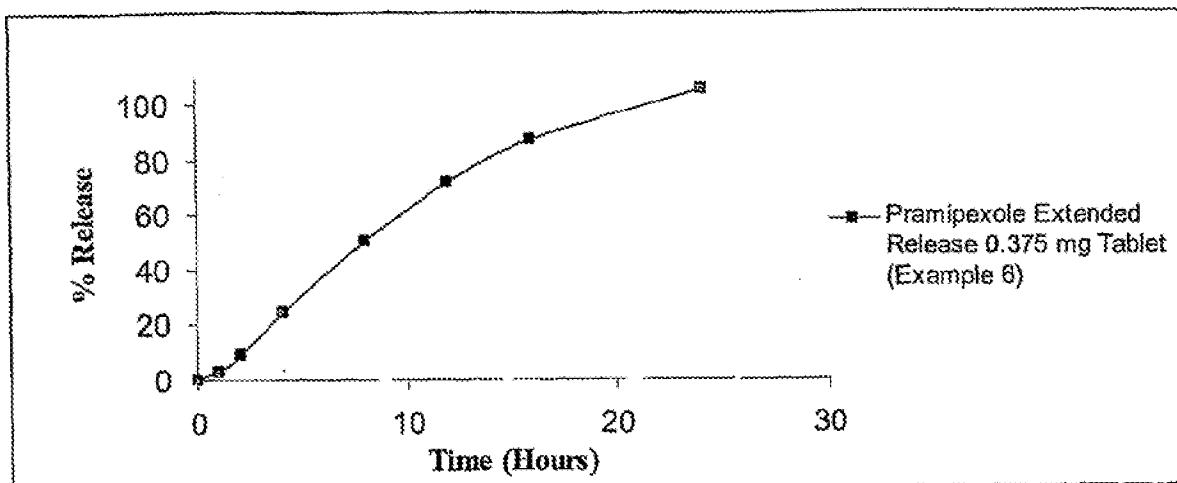


FIG. 10B

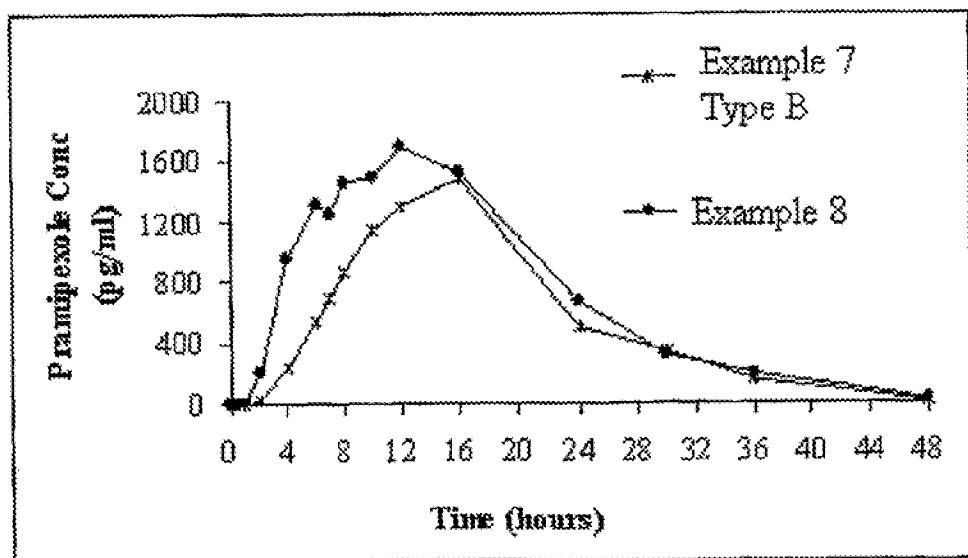


FIG. 11

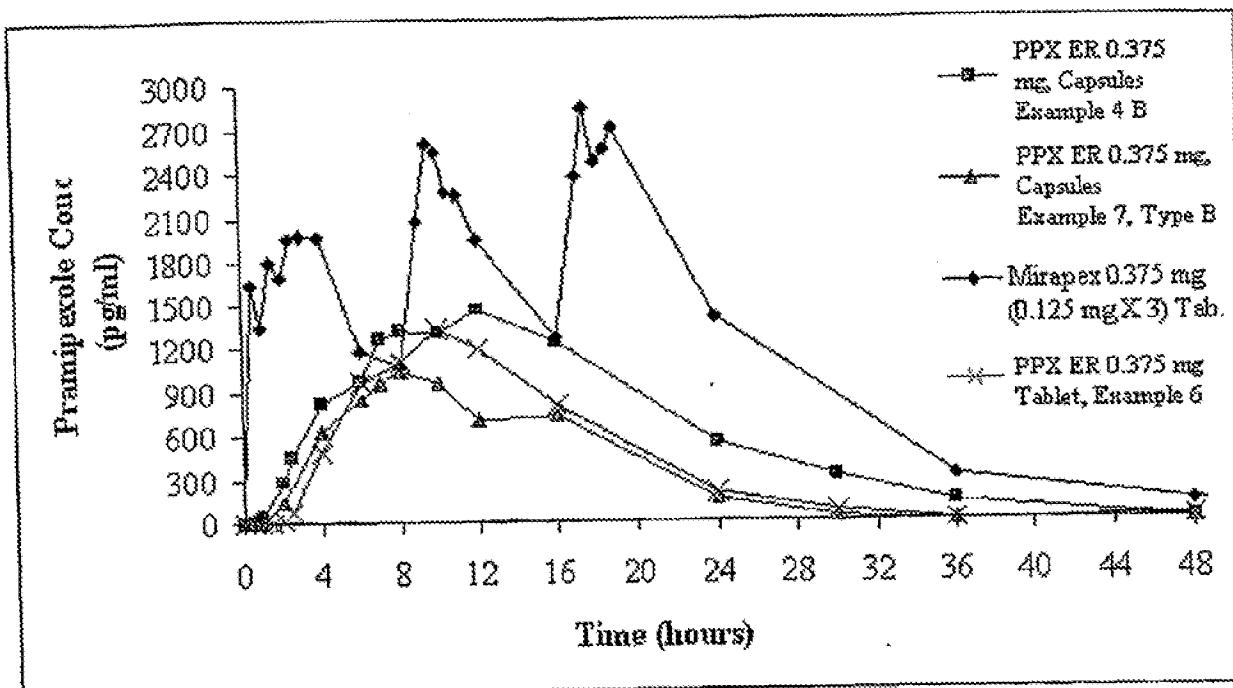


FIG. 12

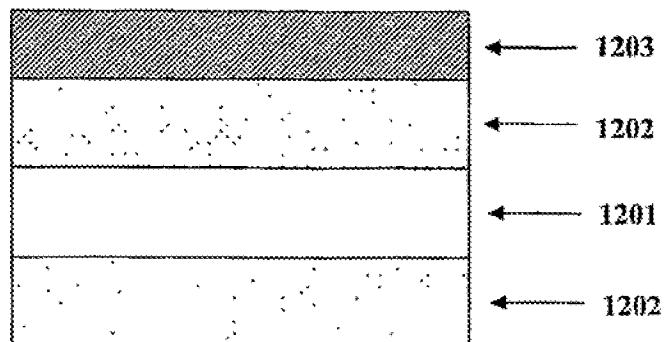


FIG. 13

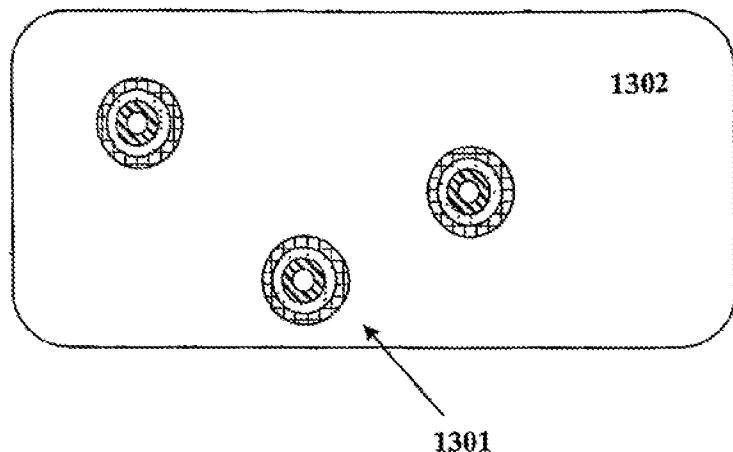


FIG. 14

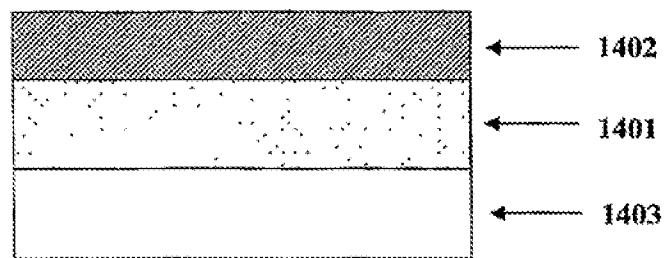
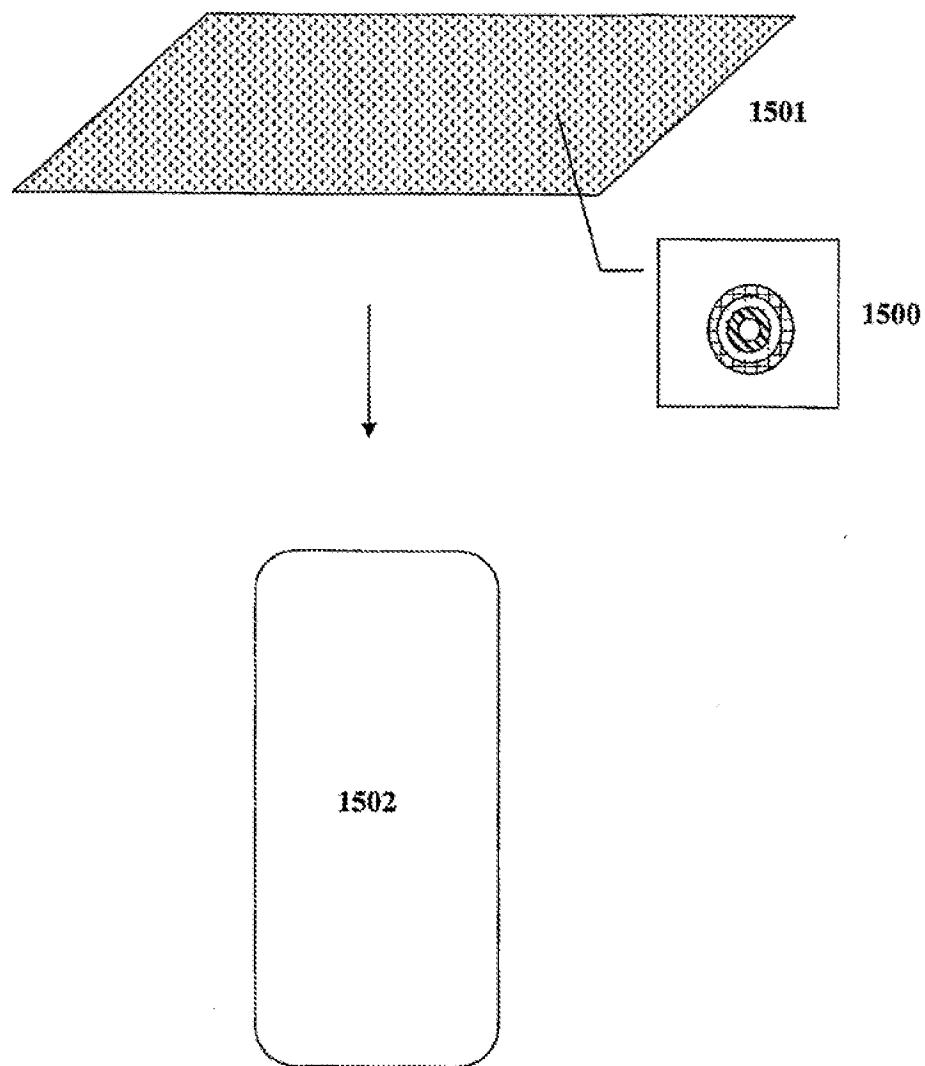


FIG. 15



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/024665

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K9/20 A61K9/28 A61K31/428

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/091585 A (SYSTHON BV [NL]; PLATTEEUW JOHANNES JAN [NL]; VAN DEN HEUVEL DENNIE JO) 28 October 2004 (2004-10-28) page 11, line 16 – page 13, line 22 examples 9,15	1-28
X	US 2003/152627 A1 (BECKERT THOMAS [DE] ET AL) 14 August 2003 (2003-08-14) abstract paragraph [0018] – paragraph [0050]	1-28
X	WO 2004/087175 A (PHARMACIA CORP [US]; NOACK ROBERT M [US]; HEIMLICH JOHN M [US]; LEE ER) 14 October 2004 (2004-10-14) paragraph [0012] – paragraph [0013] paragraph [0036] – paragraph [0044] paragraph [0052] – paragraph [0054]	1-28
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *C* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search:

12 October 2006

Date of mailing of the international search report

30/10/2006

Name and mailing address of the ISA/

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Tel. (+31-70) 340-2040, TX. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Sproll, Susanne

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/024665

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/053402 A (PHARMACIA CORP [US]; HEIMLICH JOHN M [US]; NOACK ROBERT M [US]; COX ST) 3 July 2003 (2003-07-03) abstract page 4, line 11 - page 5, line 10 page 7, line 17 page 14, line 21 - line 24 page 15, line 10 - line 11	1-28
X	WO 2005/014562 A (SYSTHON BV [NL]; VAN EUPEN JACOBUS THEODORUS HE [NL]; PICHA FRANTISEK) 17 February 2005 (2005-02-17) page 13, line 6 - line 17	1-28
X, P	WO 2005/079748 A2 (LACER SA [ES]; JURADO SANCHEZ FRANCISCO [ES]; DE PABLO SEDANO MARTA [E] 1 September 2005 (2005-09-01) abstract page 8, line 30 page 15, line 1 - line 14 examples	1-28
P, A	WO 2006/015943 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; FRIED) 16 February 2006 (2006-02-16) the whole document	1-28
A	WO 2004/010982 A (PHARMACIA CORP [US]; LEE ERNEST J [US]; HEIMLICH JOHN M [US]; NOACK RO) 5 February 2004 (2004-02-05) the whole document	1-28
A	US 2003/045539 A1 (GOMEZ-MANCILLA BALTAZAR [US]) 6 March 2003 (2003-03-06) cited in the application the whole document	1-28
A	US 2004/166159 A1 (HAN CHIEN-HSUAN [US] ET AL) 26 August 2004 (2004-08-26) cited in the application the whole document	1-28

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 28 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 3.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/024665

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